Remarks

In a previous Office Action/Restriction Requirement dated June 18, 2007, the Examiner noted that claims 1 - 20 are subject to restriction in that as filed, they allegedly cover nine (9) independent and distinctly methods of treating a variety of different unrelated medical disorders caused by different unrelated biological pathways whose treatment thereof would therefore constitute separate, unrelated inventions. Whereas Applicants, by their Attorney, elected group 1 claims 1 – 7 drawn to a method of treating a patient for sleep disorders comprising the administration of the claimed compounds of the invention, after an amendment filed on January 30, 2008, only claims 1, 3,4 and 5 remain pending.

I. Rejection under 35 U.S.C. §103

Claims 1 and 3-5 are again rejected under 35 U.S.C. 103(a) as being as being unpatentable for obviousness over the Singer et al. (1973) abstract in that it is once again asserted by the Examiner that the reference teaches that 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (also known as cyamemazine) is mainly indicated for the treatment of insomnia, psychomotor agitation, and delirium. The Examiner also maintains that the abstract teaches that the drug is used as a sedative narcoleptic in patients with a secondary psychiatric condition. The obviousness rejection is based further in view of a second article *Sleep Apnea and Cardiovascular Abnormalities* by Tilkian (1978). The Examiner based this rejection in the assumption that the patient population being treated in claim 5 is suffering from obstructive sleep apnea. It is asserted that Singer et al. teaches that 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (also known as cyamemazine) is mainly indicated for the treatment of insomnia. (abstract). However, it is also admitted that whereas the Singer et al. (1973) abstract does not teach the treatment of obstructive sleep apnea, the Tilkian abstract teaches insomnia is a symptom of obstructive sleep apnea. (abstract). It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ cyamemazine for the treatment of obstructive sleep apnea patients having insomnia because cyamemazine is effective in treatment of insomnia as taught by Singer et al. and because insomnia is a symptom of obstructive sleep apnea. One would therefore have allegedly been motivated to make such a modification in order to successfully treat obstructive sleep apnea by treating a symptom

of obstructive sleep apnea, i.e., insomnia that is effectively treatable with cyamemazine in view of Singer et al. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references. This rejection is again traversed for the same reasons as set forth in the amendment of January 30, 2008 which respectfully is a part of the record.

In the response to the final office action of May 27, 2008, Applicants submitted the following Table of comparative data which illustrated the improved properties of the claimed compounds of the present invention with the cymemazine compounds referred to in the articles cited by Examiner Kim as prior art which allegedly rendered the pending method claims obvious. However, the amendment and response submitted after final the summary was not entered into the record so Applicants once again suibmit the following summary table below comparing the respective affinities of the compound of the present invention and cyamemazine.

Receptor	**IC50 (nM)**		**Ki(nM)**	
	Cyamemazine	Compound of the invention	Cymemazine	Compound of the invention
5HT1a	1030	460	517	184
5HT2a	3.5	9.0	1.5	1.5
5HT2c	36	23	12	8.5
H1	22	22	9.3	9.3
M3	44	5490	32	3920
M 2	61	368	42	251
D2	16	31	5.8	12

The present invention comprises novel compounds known as 2-cyano-10-(2-methyl-3-(methylaminopropyl)phenothiazine (I) or a pharmaceutically acceptable salt thereof. These differ from the known chemical compound cyamemazine in the presence of a methyl ($-CH_3$) group. These have been useful as new anti-psychotic agents with an improved safety ratio. The compounds of the present invention possess a better affinity for the 5 HT1a and

5HT2c receptors as can be seen from the table above wherein the compounds of the present invention are compared vis – a – vis with their respective affinities for the receptors.

The table clearly shows that the claimed compounds of the present invention have a better affinity to both the -5HT1a and the -5HT2c receptors (those active in the treatment of anxiety and sleep disorders) and a low affinity for the M2 and M3 receptors which will result in the occurrence of less cholinergic effects such as dry mouth when the compounds are administered to a patient. Furthermore, the ratio of 5HT2a/D2 is 0.21 for cymemazine and is higher (0.29) for the compounds of the present invention. This indicates a better physiological tolerability of the compounds of the present invention than that of cyamemazine by the patient.

Therefore, the compounds of the present invention clearly have a better drug profile than cyamemazine and this property, while not only unexpected, was also highly unpredictable that the compound with this extra methyl will present such a difference in activity for 5HT1a, 5HT2c and M3 receptors.

In the Advisory Action of September 29, 2008, the Examiner asserted that the comparative data submitted in the above-referenced table was not persuasive because the evidence relied upon should clearly establish a clear and unexpected result and that "the differences in results are in fact unexpected and unobvious and of both statistical and practical significance". In a telephone interview between Examiner Kim and the undersigned attorney on October 20th, the data above which had not been made of record in the previous response was pointed out yet Examiner Kim re-iterated her point and asserted that the obviousness rejection was maintained because there was no proof that the differences in the compounds vis-à-vis receptor affinities and hence any consequential improvement in therapeutic efficacy resulting therefrom was surprising and unexpected. There was no proof that the differences in the data were statistically significant. Applicants respectfully assert that under *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, 127 S. Ct. 1727, 1741 (2007) this requirement for proof that the above - disclosed differences in the compounds' affinities for both the -5HT1a and the -5HT2c receptors as well as the M2 and M3 receptors is statistically significant in order to overcome a finding of non-obviousness is respectfully mis-placed. The Examiner has not pro-offered any explanation or evidence to support her conclusion that:

1) The difference in the numbers that represent the affinities of the compounds for the receptors and hence their therapeutic efficacy is not significant, and;

2) One skilled in the art would not be able to interpret this data and know that there **is** a statistically significant difference here between the numbers representing the different affinities of the compounds for the receptors.

Hence, the data submitted previously on August 27, 2008 and again herein is proof of the surprising and unexpected results obtained using the claimed compounds of the present invention thereby distinguishing them over those of the cited prior art. In statistics, a result is called "significant" if it is unlikely to have occurred by chance. "A statistically significant difference" simply means there is statistical evidence that there is a difference; it does not mean the difference is necessarily large, important or significant in the usual sense of the word. (See Merriam Websters Dictionary) Clearly here, a person of ordinary skill in the art would recognize that the differences in the higher values of the ratio of 5HT2a/D2 between the claimed compounds herein (0.29) and that of the cited prior art (0.21) is significant. (0.29 – 0.21 = .07; 0.07/0.29 = 0.24 = 24%) and the compounds useful in the claimed methods of the present invention are thus more therapeutically efficatious.

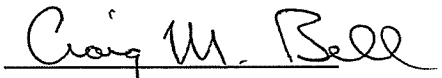
Moreover, it also would not have been obvious to combine the Singer et. al. article together with Tilkiani et. al. article under 35 U.S.C. §103 to use the compounds of the presently claimed invention in the treatment of sleep disorders and insomnia. Simply because Tilkian et. al. may suggest that insomnia or daytime sleepiness may be related to obstructive sleep apnea, one cannot presume that the cyamemazine compound disclosed in Singer et. al. will be an effective treatment of both insomnia and anxiety. For it is well established that chemistry is a highly empirical science and one can rarely predict, if ever, how one or more compounds will react when placed under similar conditions or environments or when combined with other compound(s). In re Johnson 747 F. 2nd 1456,1460; 223 U.S.P.Q.1260, (Fed. Cir.1984); In re Papesch 315 F. 2nd 381, 137 U.S.P.Q. 43 (C.C.P.A.1963) Therefore, simply because one reference may suggest the similar etiological and physiological relationships between a number of neurologically based disorders, one cannot presume a drug useful in the treatment of one will be useful in the treatment of the other. This lack of predictability is even greater in the present situation since the claimed compounds of the present application are not anticipated in the prior art. The rejection of claims 1 and 3-5 under 35 U.S.C. 103(a) as being as being unpatentable for obviousness should therefore be withdrawn.

It is therefore respectfully submitted that in light of the foregoing amendments to the claims and arguments as to their patentability, it is respectfully asserted that the

remaining pending claims now recite patentable subject matter that is clearly distinguishable and an advance over the cited prior art. It is further respectfully requested that said rejections of the claims be withdrawn so that they might pass to allowance and issue. Should however, the Examiner still have some remaining issue(s) or concern(s), he is earnestly solicited to contact the undersigned attorney so that any un-resolved matter might be overcome and resolved. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

Applicants believe there are no fees due for this response. However, if the Examiner deems that fees are due, please charge these fees to Deposit Account No. **18-1982** for sanofi-aventis, U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**. and thank your consideration and assistance in this matter.

Respectfully submitted,



Craig M. Bell
Registration No. 31,812
Attorney for Applicants

sanofi-aventis U.S.
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
MAIL STOP: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-2387
Telefax: 908-231-2626